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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/351,778
Filing Date: July 12, 1999
Appellant(s): WOLD ET AL.

Monica A. De La Paz
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 18 Nov. 2004.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is incorrect. A correct statement of the status of the claims is as follows:

This appeal involves claims 11-15, 20-22, 24, 32-44, 60-75, and 97-108, as indicated in the brief.

Claim 5 has been allowed. The brief did not identify claim 5 as having been allowed.

Claims 6-9, 16-19, 23, 25-31, and 76-84 have been withdrawn from consideration as not directed to the elected invention. The withdrawn claims are directed to non-elected inventions, rather than non-elected species as indicated in the brief.

Claims 1-4, 10, 45-59, and 85-96 have been canceled, as indicated in the brief.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct. No amendment after final has been filed.

(5) Summary of Invention

The summary of invention contained in the brief is basically correct until the last sentence on page 4. The summary is deficient because the final sentence in this section, that the GZ3 vector "is currently in preclinical development and is expected to be in the clinic in the very near future," is not present in the original specification. The statement is gratuitous and is not relevant to the issues on appeal.

(6) Issues

The appellant's statement of the issues in the brief is correct. With respect to issue (c), as noted by Appellant on page 13 of the brief, claim 10 had been cancelled and is not on appeal.

Also, the terminal disclaimer filed on 05 Nov. 2004 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of US Pat. No. 6,627,190 has been reviewed and is accepted. The terminal disclaimer has been recorded. Consequently, the double-patenting rejection set forth in the final rejection is not at issue.

(7) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Prior Art of Record

6,197,293	Henderson et al.	3-2001
6,254,862	Little et al.	7-2001

Freytag et al. "A novel three-pronged approach to kill cancer cells selectively: concomitant viral, double suicide gene, and radiotherapy," Human Gene Therapy, vol. 9 (10 June 1998), pp. 1323-1333.

Doronin et al., "Tumor-specific, replication-competent adenovirus vectors overexpressing the Adenovirus Death Protein," J. Virol., vol. 74, no. 13, (July 2000), pp. 6147-6155.

Bett et al. "An efficient and flexible system for construction of adenovirus vectors with insertions or deletions in early regions 1 and 3," Proc. Natl. Acad. Sci. USA, vol. 91 (1994), pp. 8802-8806.

Tollefson et al. " The E3-11.6-kDa Adenovirus Death Protein (AdP) is required for efficient cell death: characterization of cells infected with adp mutants, Virol., vol. 220 (1996), pp. 152-162.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 11-15, 20-22, 24, 32-44, 60-75, and 97-108 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 13, 60, 101, 102, and claims dependent therefrom recite "method for treating cancer in an animal having a tumor." Appellant had not indicated in the reply of 08 Dec. 2003 where support for this limitation, in particular recitation of "animal," is supported by the original

specification. It is Applicant's burden to indicate where such support may be found. See MPEP 714.02, last sentence of the third paragraph from the end and 2163.06 (I) last sentence.

Animals include organisms from protozoans to sponges and on up to mammals. It is unclear that simple animals even develop anything one would call cancer. Page 1, line 10 states that the vectors of the invention are for treating human cancer, and the specification refers to treating cancer in "patients," which when read in light of page 1, line 10, would be human patients. It is unclear that the original specification teaches using the method to treat cancer in mammals generically, much less extending to other animals as recited.

With respect to claim 13 and its dependent claims, claim 13 has been amended to include the limitation that overexpression of ADP is defined by overexpression of ADP by the adenovirus vector relative to dl309. Applicant indicates the new limitation is supported by page 5, lines 18-22; page 12, lines 18-21, and Example 1. However, dl309 is not wild type, and there is no evidence that dl309 expresses ADP as high as any previously known adenovirus, nor was expression of ADP in dl309 or KD and GZ vectors measured as molecules of ADP per viral genome, as per page 12, lines 18-21. With respect to Example 1 of the specification, these portions of the original specification describe characterization of the disclosed KD and GZ vectors, and comparison of ADP expression of A549 cells transfected with each these vectors or with dl309, *dl*01/07, and dl327 *inter alia*. KD vectors are compared to dl309 as well as to *dl*01/07, and GZ vectors are compared to *dl*01/07 as well as to dl309 at 24 hour post-infection. However, at 36 hour post-infection KD vectors are compared only to *dl*01/07 and GZ are compared only to *dl*309. This description only refers to the KD and GZ vectors, and does not describe such a comparison as being generally determinative of an adenovirus vector

overexpressing ADP. There is no mention, even in passing, of applying the standard for overexpression recited in claim 13 to the invention as originally described, which includes adenovirus where ADP expression is increased by means other than removing splice sites and E3 coding sequences as in the KD and GZ vectors, see page 13, lines 2-8. At best, the claim limitation applies only to embodiments involving the KD and GZ vectors.

Claim 32 recites that ADP overexpression "is detectable by western blot, cell lysis, virus release, or by cell spreading assay." Claims 103-106 recite these individually. Applicant indicates that Fig. 2 and Example 2 support this limitation with respect to cell lysis or cell spreading assay. However, Example 2 does not teach that any of these methods are to be used to determine whether ADP is overexpressed. Instead, these assays were used to characterize KD1 and KD3 infection, and the consequence of ADP overexpression. Example 2 discloses that overexpression of ADP in the case of KD1 and KD3 leads to an increased rate of cell lysis, more rapid virus release, and increased cell spreading as compared to dl309, *dl*01/07, and Ad5. It does not suggest that either assay is to be used to determine whether ADP is overexpressed by a given adenovirus vector used in the invention. While ADP overexpression may lead to increased rate of cell lysis, virus release or cell spread, it does not follow that an increased rate of cell lysis or cell spread displayed by an adenovirus vector, whose level of ADP expression is unknown, means the adenovirus vector overexpresses ADP, as is implied by the claim limitations.

Taking a characteristic of an individual embodiment and making that characteristic the basis of a generic claim without further supporting disclosure is not in compliance with the written description requirement. See *Purdue Pharma L.P. v. Faulding Inc.*, 56 USPQ2d 1481,

1487 (CAFC 2000). Consequently, there is no evidence that Applicant contemplated the instantly claimed genus at the time the original specification was filed.

With respect to claim 60, and its dependent claims, claim 60 recites a series of four structural features (a)-(d) characterizing the "adenovirus vector." In particular it recites "a) …; b) …; c) …, and/or d) …". The inclusion of "and/or" indicates that at least one of these characteristics is present or all four of the characteristics are present. Applicant indicates that these limitations are supported by the specification at page 12, lines 33-35 and page 13, lines 2-8. However, the original specification presents these four characteristics as alternatives for achieving ADP overexpression. It does not teach or even imply including more than one of these alternatives within a single adenovirus vector, as would be the case where a), b), c), and d) were included. This part of the rejection would be overcome by replacing ", and/or" with --; or --. (The comma should be a semi-colon in any event).

Claims 101-102 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 101 and 102 each recite the phrase "overexpresses an adenoviral death protein," which renders these claims unclear as to the metes and bounds of the adenoviral vector. It is unclear in what context "overexpresses" is directed or applied to (i.e. overexpresses relative to what?). Wild-type adenoviruses typically "overexpress" ADP at very late stages of the infection cycle. Thus, a reasonably broad interpretation of these claims would suggest any adenovirus

carrying ADP operably linked to its native promoters, and subject to natural expression control would inherently meet the limitation of the claims as written.

Claims 11-13, 32-44, 60, 61, 68, 69, 72-75, 97-99, and 101-108 stand rejected under 35 U.S.C. 102(e) as being clearly anticipated by either Henderson et al. (U.S. 6,197,293, filed 3/02/98), or Little et al. (U.S. 6,254,862, filed 3/02/98) for the reasons of record set forth in the previous Office actions, reproduced below.

The disclosures of Henderson and Little are very similar, especially as regards ADP-expressing adenovirus vectors. Both generally describe adenovirus vectors (Ad5), which replicate in neoplastic cells, and their use in treating neoplastic tissue or cells *in vivo*, e.g. treatment of neoplastic tissue or cancer. The adenovirus vectors comprise tissue or tumor specific promoters operably linked to one or more adenoviral genes, such as ADP, E1A or E1B.

Henderson and Little each disclose replication-competent vectors which express an adenovirus death protein. They teach that the preferred ADP has the sequence of SEQ ID NO:6 (SEQ ID NO:22 in '293; SEQ ID NO: 23 in '862)) and further discloses methods of using the above recombinant vector for promoting death of neoplastic cells in tumors. Henderson teaches the use of vectors comprising prostate-specific response elements, including PB- or PSA-TREs operably linked to adenoviral genes essential for replication (such as E1 and/or E1B) to preferentially kill cells wherein the PB-TRE is active, such as prostate carcinoma cells or androgen receptor-producing cancer cells (see e.g. abstract and col. 18, lines 27-41). Henderson et al. further teaches that to ensure cytotoxicity further, one or more transgenes having a cytotoxic effect may also be present and under selective transcriptional control to provide higher

confidence that the target cells will be destroyed, and teaches the use of vectors expressing ADP as a preferred embodiment (col. 18, lines 53-61). Little teaches the use of vectors comprising alpha-fetoprotein (AFP) response elements operably linked to adenoviral genes essential for replication (such as E1 and/or E1B) to preferentially kill cells wherein the AFP element is active, such as hepatocellular carcinoma and other neoplastic cells (see e.g. abstract, col. 13, line 53 through col. 14, line 7, and col. 19, lines 31-47). Little et al. further teaches that to further ensure cytotoxicity, one or more transgenes having a cytotoxic effect may also be present and under selective transcriptional control to provide higher confidence that the target cells will be destroyed, and describes the use of vectors expressing ADP as a preferred embodiment (col. 14, lines 10-18).

Within the context of replication-restricted adenoviral vectors, both patents teach embodiments where the ADP is retained. It may be maintained within an E3 region deleted for coding sequences for the other E3 genes, optionally including the Y-leader, under control of the MLP and E3 promoters, or may be inserted into a different adenoviral region, such as E4. Alternatively, it may be placed under control of a second tissue specific promoter or a heterologous viral promoter (col. 27, lines 33-63 in '293; col. 21, line 63 to col. 22, line 29 in '862). In addition Little teaches including multiple copies of ADP coding sequence (col. 22, lines 45-60).

Henderson and Little both describe plasmids for introduction into replication-restricted adenovirus vectors of an E3 region deleted for all E3 coding sequences except for the ADP, both with and without the E3 Y leader (Figs. 5A & 5B in both; Example 4 in '293; Example 5 in '862). Both (Example 6) describe a replication-competent adenovirus vector, CN751, comprising

such an E3 region (with the Y leader). CN751 is wild type outside the E3 region (otherwise identical to CN702), and is very similar to GZ1. CN571 kills cells more efficiently and releases 10-40 times more virus at 48-72 hours post-infection as compared to a replication competent adenovirus lacking ADP. Applicant has indicated on the record (response filed 1/10/02, page 7) that CN751 would be expected to overexpress ADP.

Both teach including coding sequence for an anticancer gene product, such as a prodrug converting enzyme, ricin, factors which initiate apoptosis, Fas, IL-1, -2, -6, -12, M-CSF, IFN-γ, *inter alia*. (col. 27, lines 9-32 in '293; col. 21, lines 39-62 in '862).

With respect to claims dependent from claim 13, absent evidence to the contrary, placing ADP expression under control of a heterologous promoter (tissue specific or viral promoters) or inclusion of multiple copies of ADP would be expected to result in overexpression compared to dl309, at least at times early after infection when dl309 expresses little ADP. Claim 60 does not require overexpression of ADP.

Claims 13 and 20-22 remain rejected and claims 60 and 64-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Henderson et al. (U.S. 6,197,293, filed 3/02/98), or Little et al. (U.S. 6,254,862, filed 3/02/98) as applied to claims 10-13, 32-44, 60, 61, 68, 69, 72-75, 85-87, 89-91, 94-99 above, and further in view of Freytag.

Henderson and Little have been described.

Freytag et al. discloses a novel three-pronged approach to kill cancer cells selectively comprising administration of a cytolytic replication-competent, E1B-attenuated adenovirus in conjunction with chemotherapy (i.e. suicide gene therapy employing virally encoded cytosine

deaminase in conjunction with 5-FC) and radiation (see e.g. abstract and Fig. 8). Freytag teaches that the results demonstrate that "suicide gene therapy can enhance the therapeutic effects of viral therapy in a tumor cell-specific manner..." and that "[T]he therapeutic effect of these combined modalities can be further enhanced by coupling them with radiotherapy" (p. 1328, right col.). Freytag further teaches that "because few human cancers are curable with a single modality, it has been our tenet that the promise of cancer gene therapy will be realized only when used in combination with other modalities, such as the ones described here" and would offer "a significant improvement over ONYX-015 because the three modalities may target different tumor cell types or subpopulations, which, in turn, should expand the spectrum of human tumors that it will be effective against" (p. 1330, left col. and p. 1332, last paragraph).

At the time the invention was made it would have been obvious for one of ordinary skill in the art to combine the chemotherapy/radiation combination approach of Freytag when using the replication-competent adenovirus vectors of Henderson or Little, since Freytag teaches the enhanced cell killing properties when using a three-pronged approach involving additional modalities, combining a replication-competent adenovirus in conjunction with chemotherapy and radiation. Thus the invention was prima facie obvious at the time the invention was made.

(10) Response to Arguments

Response to arguments in section VII.A.1.a).

The Examiner concurs with Appellant. The grounds of rejection for recitation of "in an animal having a tumor" does not apply to claims 107 and 108, which limit the invention to humans having tumor, which is supported by the original specification.

Response to arguments in section VII.A.1.b).

Appellant argues that the specification would indicate to the skilled artisan that treatment of animals was contemplated because: 1) the specification at page 17, lines 16-21, teaches that the methods "are useful for killing neoplastic cells of any origin"; and 2) Examples 4 and 8 demonstrate the treatment of mice having tumors, with mice being referred to as animals (page 27, lines 20-21).

With respect to the first point, "neoplastic cells of any origin" in the cited paragraph on page 17 refers to the origin of neoplastic cells within the patient referred to in the paragraph, not to the origin of the patient. Also, the claims are directed to a method of treating cancer in an animal having a tumor, not to killing neoplastic cells in general. While cancerous tumors comprise neoplastic cells, not all neoplastic cells originate from tumors associated with cancer. Neoplastic cells are any proliferating abnormal cells, including cells in benign tumors, and are not limited to cells in tumors.

With respect to the second point, a nude mice having implanted cells from a human cancer cell line, A549, is an experimental models of human cancer, as indicated on page 27, lines 20-21, of the specification, and is not a mouse (animal) suffering from cancer. Cancer involves pathogenic, abnormal proliferation of cells originating in the animal. Rather, this model is more

akin to disease caused by an infectious agent, the human cancer cells, which has been used as an approximation of cancer. That the specification refers to such mice as an "animal model" for the growth of human tumors cannot be construed as a teaching that the claimed method was contemplated to extend beyond humans to mice or other animals. While it is true that animals can be patients, e.g. pet dogs and cats, there is no indication that "patient" as used in the specification refers to anything other than human patients. The specification at page 1, lines 8-10, could not be more clear that the vectors are used to treat human cancer specifically, and not animal cancer in general. Page 27, lines 20-21 reinforces this assessment by describing the mouse model as a model for the growth of "human" tumors.

Response to arguments in section VII.A.2.

Appellant asserts that whether *dl*309 is a wild type adenovirus or not, or whether it expresses ADP as high as any previously known adenovirus is irrelevant to the written description issue, noting that the specification teaches that *dl*309 expresses wild-type levels of ADP.

In response, this is germane to the written description issue because the specification (page 12, lines 19-21) specifically defines "overexpresses ADP" to mean "that more ADP molecules are made per viral genome present in a dividing cell infected by the vector than expressed by ***any*** previously known recombinant adenoviral vector or AAV in a dividing cell of the same type" (emphasis added). The phrase "than expressed by any previously known recombinant adenoviral vector" clearly means that the adenoviral vector used in the claimed method must express more ADP per viral genome than would the known adenoviral vector that produces the most ADP per viral genome of any of the known adenoviral vectors. That *dl*309

produces wild type levels of ADP, generally, is not an indication that it produces more ADP per viral genome than any other previously known adenoviral vector, and that it alone among the previously known vectors is the standard against which the adenoviral vectors used in the claimed method are to be measured. It is further noted that *dl*309 is not a recombinant adenoviral vector; it is a mutant adenovirus.

Appellant argues that the use of *dl*309 in the examples, when read in light of the definition on page 12, lines 18-23, would indicate that *dl*309 was "intended to be a standard against which one can measure overexpression," since *dl*309 was one of the previously known adenoviruses to which the KD and GZ vectors were compared. Appellant then poses the question "[W]hy else were these vectors chosen and presented as ADP expression controls and included as such in virtually all the examples?"

In response, the specification does not teach that any one adenovirus is the yardstick, even in the case of the KD and GZ vectors, comparison was made to several adenoviruses that were close in structure to the KD and GZ vectors. In the general discussion, the specification indicates that the measure would be ADP molecules per viral genome against all previously known adenoviruses (page 12, lines 18-21), not against any one adenovirus chosen in hindsight after the application was filed. Also, the specification does not disclose that the KD and GZ vectors were compared to any adenovirus in terms of directly measured ADP molecules per viral genome, as set forth in the definition; nor has Appellant provided any evidence that these vectors have ever been compared to other adenoviral vectors in this manner. Thus, the question of whether the KD and GZ vectors "overexpress ADP" according to the definition on page 12 is unresolved.

In addition, while the specification shows that early after infection, ADP is expressed in higher amount with the KD and GZ vectors than *dl*309, for example, late in infection ADP levels in KD, GZ, and *dl*309-infected cells were comparable (Fig. 2). Also, Doronin (page 6150, col. 1) discloses that the level of ADP expressed in dividing A549 cells infected with KD1 or KD3 was "perhaps a little more than *dl309*" (emphasis added), i.e. it was equivocal whether the KD vectors expressed more ADP. In order for ADP levels in *dl*309 to have risen to comparable levels at the later time point, ADP expression in *dl*309 must have exceeded that of the KD and GZ vectors at later during infection. The heading of Figure 2 indicates the most salient result - the E3 deletions in the KD and GZ vectors cause deregulation (not up-regulation as stated in the brief) of ADP expression, such that ADP is expressed earlier in the infection cycle.

Furthermore, if *arguendo* one of skill would glean from the examples that *dl*309 was to be used as the standard for assessing overexpression of ADP, then one would have also gleaned that A549 cells, specifically, should be used as the dividing cell. The amended claims do not limit the comparison to one made in A549 cells. Appellant is picking and choosing among the specific details of the examples to form the basis for a generic claim, where the original specification never generically presented any of the specifics in isolation from one another as being the basis for generic embodiments.

As to the question posed by Appellant, the specification does not explain why these strains were chosen to compare the KD and GZ vectors. One of skill in the art is left to guess the answer. The Examiner guesses that *dl*01/07 and *dl*309 were chosen because they are genetically identical to the KD and GZ vectors, respectively, except for the deletions in the E3 region.

Finally, in subsection b), Appellant dismisses the fact that the examples do not describe measurement of ADP expression as molecules of ADP per viral genome as being irrelevant to the written description issue. However, the specification (page 12, lines 19-21) specifically defined "overexpresses ADP" in these terms, so this issue is germane to whether a given vector overexpresses ADP. Without the normalizing ADP amount against the amount of viral genome in the infected cells, one cannot determine whether the KD or GZ vectors resulted in an overexpression of ADP over the infection cycle relative to another adenovirus, for example, from the results of a Western blot such as shown in Figure 2. Comparison of the amount of ADP produced by infection of each of the adenoviruses to the amount of viral genome present in the infected cells allows one to make a meaningful comparison. Otherwise, experimental differences and differences in replication rate, for example, are not corrected for. Experimental differences could include differences in the fraction of viable virus in the preparations of the different adenoviruses used to transfect the cells, and differences in the amount of virus actually delivered to the cells. A higher replication rate for one adenovirus as compared to another would produce more viral genomes and thus copies of ADP coding sequence per unit of time, and may produce a higher absolute level of ADP as compared to another adenovirus due to a higher copy number of ADP coding sequence, even if the level of ADP expressed per viral genome (or per copy of ADP coding sequence) were lower than that of the different adenovirus.

Response to arguments in section VII.A.3.

Appellant argues the limitation that ADP overexpression “is detectable by western blot, cell lysis, virus release, or by cell spreading assay” is supported in the original specification because the examples showed that ADP is required for efficient lysis of infected cells, and that

higher expression of ADP increased cell lysis. In response, the issue here is not whether the specification disclosed that increased cell lysis, virus release and cell spreading are consequences of ADP overexpression, but whether the specification taught that increased cell lysis, virus release and cell spreading means that the adenovirus overexpresses ADP. The specification does not teach generally or specifically that increased cell lysis, virus release and cell spreading means that the adenovirus overexpresses ADP. Nothing in the specification indicates that the only cause for increased cell lysis, virus release and cell spreading with respect to an adenovirus is that ADP is being overexpressed. Appellant is putting the cart before the horse here. Appellant's argument is analogous to arguing that since fire results in oxidation, then if oxidation has occurred the cause was fire. However, hydrogen peroxide, for example, can cause oxidation without fire.

Appellant has provided no argument as to how "detectable by Western blot" is supported by the original specification. The Examiner notes that the Western blot results are not normalized to the amount of viral genome in the cells. Consequently, this measures only the absolute amount of ADP in the cells, and not the amount of ADP per viral genome, which is the standard for measuring ADP overexpression set forth in the specification (page 12, lines 19-21).

With respect to *Purdue Pharma*, Appellant argues that this case is misapplied here because the specification teaches these as ways to identify a vector that overexpresses ADP. However, the original specification does not teach that ADP overexpression in an adenoviral vector is to be determined by "western blot, cell lysis, virus release, or by cell spreading assay." This limitation was gleaned from the examples, which present these as assays to characterize the consequence of ADP overexpression, not assays diagnostic of ADP overexpression. The

standard set forth in the specification is set forth on page 12, lines 19-21, measuring ADP molecules produced per viral genome in a given dividing cell.

Response to arguments in section VII.A.4.

Appellant argues that the connector "and" on page 13, line 5, implies that the characteristics are cumulative and combinable. In response, the connector "and" used on page 13, lines 2-8, does not imply that the alternatives are to be combined. Page 12, line 32, to page 13, line 8, lists some of the "multitude of ways" that ADP overexpression may be accomplished. Page 12, line 33, to page 13, line 2, lists one way - deleting splice sites from the E3 region, as in the KD and GZ vectors. Then page 13, lines 2-8, lists "other means" than deleting splice sites. This paragraph never suggests that these "ways" or "means" should be combined, much less that all of them should be combined, as recited in claim 60 with respect to "and".

Response to arguments in section VII.B.

Appellant argues that the definition of "overexpresses ADP" on page 12, lines 18-23, is clear. This definition requires that ADP made from the vector recited in the claims produce more ADP molecules per viral genome "than expressed by any previously known recombinant adenoviral vector." The definition does not specify any time frame in which such a measurement must be taken, e.g. over the life cycle, at early stages of infection, at late stages of infection, etc.

Appellant has argued in section VIII.A. of the brief that the original specification supports claims, e.g. claim 13, limited to comparing the ADP expression of the recited vector to *dl*309. Appellant has argued that the examples support an interpretation of the definition on page 12 that the comparison be made to *dl*309. However, such a comparison was also made to *dl*01/07 in these same examples. By Appellant's logic in section VIII.A., comparison can alternatively be

made to *dl*01/07, since it was used for such a comparison. As shown in Fig. 2, *dl*309 produced more ADP than did *dl*01/07. Thus, some vectors, e.g. *dl*309, excluded from the claim when comparing to *dl*309 would be included when comparing to *dl*01/07. Since the choice of reference vector is left to one of skill in the art and different previously known vectors produce different amounts of ADP, then the metes and bounds of claims 101-102 are subjective.

On the other hand, if the definition on page 12 means that the vector used in the method of claims must produce more ADP than <u>every</u> previously known adenovirus vector, then one of skill in the art must known exactly which vector of all previously known adenovirus vectors produces the most ADP in a given dividing cell. This vector may or may not be *dl*309. The specification does not identify the previously known adenovirus vector that produces more ADP per viral genome than any other.

Response to arguments in section VII.C.1.a.

It should be kept in mind that the claims under discussion here are directed to a <u>method</u> of treating cancer with a replication competent adenoviral vector that <u>overexpresses</u> ADP. Appellant asserts that Examiner has presented no evidence that the vectors taught in Henderson and Little would overexpress ADP. While it is true that neither patent states that the vectors overproduce ADP, the vectors they describe have structural features that the instant specification teaches would cause ADP overexpression. By the same token, Appellant has presented no evidence that the KD and GZ vectors overexpress ADP when ADP expression is measured as molecules of ADP per viral genome. It is clear that these vectors express significantly more ADP in the culture (as opposed to per viral genome) early in infection than does *dl*309, for example. It

remains equivocal whether they produce more ADP in the culture over the entire infection cycle (see response to brief section VII.A.2).

CN751 (Henderson, Ex. 4; Little, Ex. 5) comprises no E3 coding sequence other than for ADP, and lacks most, if not all, of the same splice sites missing from KD1, KD3, GZ1, and GZ3. CN751 comprises the E3 deletion of BHG11 into which were inserted Ad2 nucleotides 28287-28622 (untranslated Y leader) fused to Ad2 nucleotides 29195-29872 (Ad2 ADP coding sequence). Bett et al. (at page 8803, col. 2) discloses that BHG11 has a deletion of Ad5 E3 nucleotides 27,865-30,995. Consequently, CN751 lacks all Ad5 E3 coding sequence and has the Ad2 ADP coding sequence. The location and extent of the deletions in CN751 is very similar to that of KD1 and GZ1 (see spec., Table 1). Henderson (col. 27, lines 43-63) and Little (col. 21, line 63 to col. 22, line 29) both teach that the Y leader segment may be omitted. The resulting adenovirus would lack even more E3 sequences than does KD1, KD3, GZ1 or GZ3. Thus CN751 and the derivative lacking the Y-leader segment comprise deletions that would remove most, if not all, E3 splice sites. The specification (page 12, lines 33-35) teaches:

> In general, any type of deletion in the E3 region that removes a splice site for any of the E3 mRNAs will lead to overexpression of the mRNA for ADP, inasmuch as more of the E3 pre-mRNA molecules will be processed into the mRNA for ADP.

By this criterion, set forth in the specification, the Office has sound reason to believe that CN751 overexpresses ADP, and the burden shifts to Appellant to prove otherwise. *In re Spada*, 15 USPQ2d 1655, 1658 (CAFC 1990).

In addition to CN751, Henderson and Little disclose other types of ADP producing vectors. Some of these would be expected to "overproduce" ADP relative to an adenoviral vector with an intact E3 region containing the ADP coding sequence under its normal regulatory

sequences. For example, Henderson (col. 27, lines 57-63) and Little (col. 22, lines 20-29) teach placing the ADP coding sequence in a different region of the adenoviral genome or under control of a heterologous promoter, such as a viral promoter. Henderson (col. 17, lines 11-15) and Little (col. 11, lines 45-50) teach the SV40 promoter as such a heterologous viral promoter. This promoter is widely used in molecular biology, and is known to be a strong constitutive promoter. Other means taught in the instant specification (page 13, lines 1-8) that causes overexpression of ADP are placing the ADP coding sequence in other regions of the adenoviral genome and placing it under control of a heterologous promoter, e.g. the CMV promoter, which like the SV40 promoter is a strong constitutive viral promoter. In addition, Little (col. 22, lines 45-55) teaches to include multiple copies of ADP coding sequence in the vector. Clearly, one would expect a vector with two or more copies of ADP coding sequence to express more ADP than a vector with one copy.

Response to arguments in section VII.C.1.b.

Appellant asserts that Henderson and Little teach CN751 expresses the same amount of ADP as does wild-type adenovirus. Appellant does not indicate where either patent contains such a teaching, nor was the Examiner able to find such a teaching. Appellant argues the teachings in Henderson and Little that the efficiency of killing infected cells with CN751 is "similar to" Rec700 means that CN751 produced wild-type levels of ADP. First, of all, the experiment shown in Henderson and Little is not the same as any experiment carried out by Appellant. Second, the comparisons are to Rec700 not *dl*309, and Appellant has not shown that Rec700 and *dl*309 produce the same amount of ADP. Therefore, Appellant is comparing apples with oranges here. In addition, "overexpresses ADP" does not require a dramatic difference in ADP expression, it

merely requires that more ADP molecules per viral genome be produced. Even if the additional production averages a small fraction of a molecule of ADP produced per viral genome when compared to a previously known adenoviral vector, the vector would be readable on the claims. By stating "similar", Henderson and Little are making a qualitative comparison, not a quantitative comparison, i.e. it cannot be determined whether the cell killing by Rec700 was slightly lower, slightly higher or exactly the same as killing by CN751. All one can conclude from Henderson and Little is that the killing by CN751 was more like that of Rec700 than of the vector lacking ADP coding sequence.

In Example 4 of the instant specification (page 28), weekly inoculation of tumors in nude mice with *dl*309, KD1 or KD3 lowered the growth rate of the tumors by about the same extent, such that the tumors grew only 2.5-fold over five weeks (Fig. 8A). With single higher dose of KD3 or GZ3, tumors grew about 8-fold over five weeks (Fig, 8B). Little presents a similar experiment where tumors in nude mice were treated with a single dose (lower than that used in Appellants experiments) and observed no growth over five weeks of tumors inoculated with CN751, and in 64% of tumors, regression was observed (col. 40, line 55, to col. 41, line 7). Little attributed the results to increased cell killing mediated by ADP, as compared to a vector lacking ADP expression. If ADP expression is responsible for the lack of tumor growth when CN751 was used, then one might conclude that since CN751 was more effective at cell killing than the KD or GZ vectors, which inhibited but did not prevent tumor growth over the same time period, then CN751 produced more ADP than the KD or GZ vectors. However, one would be ill advised to draw such a conclusion because Appellant used A549 cells for the xenografts, whereas Little used LNCaP cells. As with Appellant's indirect comparison of the results of one type of

experiment with those of a different type, such a comparison of the tumor model experiments would also be comparing apples to oranges.

The only way to resolve whether CN751, or the KD or GZ vectors for that matter, "overproduces ADP" according to the definition provided in the specification is to measure ADP produced per viral genome by CN751, KD1, KD3, GZ1, and GZ3 and by the previously known adenoviral vector that produces the highest ADP levels in the same dividing cells. Henderson and Little give precise description as to the structure of CN751, so even if CN751 cannot be obtained from them, it could be made *de novo*. Appellant has had ample opportunity to make such a comparison but has chosen not to do so.

The remaining argument presented in this section has been addressed above in the Examiner's response to the arguments presented in section VII.C.1.a. Henderson and Little teach using the SV40 viral promoter, which, like the CMV promoter taught in the instant specification, is a strong constitutive promoter.

Response to arguments in section VII.C.1.c.(1).

Appellant argues that Exhibit B in the first Wold declaration, filed 06 Jan. 2003 (Exhibit 4 of the brief) presents the inventors' goal of preparing adenovirus vectors that overexpress ADP (E3-11.6K protein). In response, this research proposal does not indicate that adenoviral vectors <u>overproducing</u> ADP are a goal. Section B of Exhibit B (page 3 of the exhibit) states that the goals are to determine whether the 11.6K protein alone "can *function autonomously* to kill cells," (emphasis in original) and to develop means for delivering the protein to cells of interest. This section does not mention that adenoviral vectors are a goal. Of further note in this section, it is stated that the 11.6K protein "has the potential use as a therapeutic agent to kill cell, e.g.

malignant cells, in humans," and that the proposed research is directed to addressing "two issues that must be resolved in order for the 11.6K protein to be used as a therapeutic agent." The therapeutic agent in the claimed method is an improved replication-competent adenoviral vector with an improvement - it overexpresses ADP. ADP itself is not the therapeutic agent, and the present specification presents no evidence that ADP alone "can *function autonomously* to kill cells."

Appellant then refers to page 6 of Exhibit B of the declaration, and summarizes plans to construct a replication-defective adenoviral vector having E1A, E1B, E3 regions deleted, and the 11.6K protein coding sequence under control of a CMV promoter. Appellant then refers to page 7, section C.3. This section describes experiments to be conducted IF it is found that the "11.6K protein alone cannot promote cell death". It describes inserting the 11.6K gene into *dl*7001, which differs from wild-type by deletion of the E3 region, i.e. it is replication competent, and then mutating adenoviral genes outside of the E3 region to map other adenoviral genes whose product collaborate with the 11.6K protein to promote cell death. Appellant asserts the such vectors "are, in essence, the principal exemplary embodiments of the present invention". In response, the claims are directed to a method for treating cancer, not to a vector, and the vector is replication competent, not replication defective as are the vectors described on page 6 of Exhibit B. Furthermore, the exemplary vectors, KD1, KD3, GZ1, and GZ3, have the ADP coding region under control of the same adenoviral promoters and polyadenylation signal(s) as control ADP expression in nature, and no splicing signals. The CMV and SV40 sequences are not present. Section C.3. does not propose using any vector made in the mapping experiments as a therapeutic agent, the goal here is quite different.

Appellant then refers to section D (page 8) of Exhibit B, "possible future experiments" (emphasis added) included to "explore ... whether a nondefective vector might be useful." This statement does not demonstrate conception of the claimed method, since clearly the author of the proposal did not know whether nondefective vectors would be useful. In fact, on page 5 (last paragraph) of Exhibit B, the author states that the eventual adenovirus used to promote cell death "should probably be defective," which nearly teaches away from the claimed invention. While conception is the mental part of the inventive act, it must be capable of proof, such as by demonstrative evidence or by a complete disclosure to another. Conception is more than a vague idea of how to solve a problem. The requisite means themselves and their interaction must also be comprehended. See *Mergenthaler v. Scudder*, 1897 C.D. 724, 81 O.G. 1417 (D.C. Cir. 1897).

Of the evidence attached to the first Wold declaration (Exhibit 4 of the brief), only Exhibit B describes adenoviral vectors as being used to kill neoplastic cells. The focus of the research proposed was delivery of the ADP protein, not necessarily using an adenovirus, and the adenovirus conceived "should probably be defective". The proposal does not suggest that the author knew which, if any, of the vectors or delivery methods described would prove useful for treating cancer, or even whether the 11.6K protein would be therapeutic when delivered by any means. Significantly, there is no indication that overexpression of ADP from a replication competent vector was even conceived for testing, much less that such a vector should be used to treat cancer.

The remaining exhibits of the declaration provide no nexus between the research proposed in Exhibit B of the declaration and the experimental results provided by the other

exhibits attached to the declaration. The remaining exhibits do not demonstrate conception of the claimed invention before the effective filing dates of Henderson or Little.

Response to arguments in section VII.C.1.c.(2)-(4).

Appellant (subsection (2)) then turns to evidence that KD1 was conceived and reduced to practice before the effective filing dates of Henderson and Little. Appellant (second bullet, page 18) characterizes paragraph 5 of the first Wold declaration showing "the observation that when target cancer vectors ..." (emphasis added) referring to bullet point three of paragraph 5. This paragraph describes the results of plaque assays (Exhibits A3-A17) on various adenoviral mutants, and no conception of using any such mutant to treat cancer. Exhibits A3-A17 show raw experimental data, with no explicit indication as to why the experiments were being performed or what declarant planned to do with the mutants in the future.

The Examiner concurs that the KD1 vector was conceived and made prior to the effective filing date of the Henderson and Little patents. However, the claimed invention is directed to a method for treating cancer with a generic replication competent adenoviral vectors that overexpress ADP. In subsection (3), Appellant points to paragraphs 7 and 8 of the first Wold declaration. Paragraphs 7 and 8 of the declaration show it was on or about 5/20/97 that declarant was aware that KD1 "overexpresses ADP," which is after the effective filing date of the Henderson and Little patents. Consequently, declarant could not have conceived of using KD1 as an adenoviral vector that overexpresses ADP in a method of treating cancer prior to the effective dates of Henderson and Little. Furthermore, there is no evidence in paragraphs 5-8 of this declaration to suggest that declarant was making the KD1 vector for the purpose of treating cancer, contrary to Appellants assertion, much less that Appellant had conceived to a method of

using a generic replication defective adenoviral vector that overexpressed ADP in treating cancer.

In subsection (4), Appellant points to the second Wold declaration as demonstrating successful testing of KD1 in an animal cancer model (these animals do not have cancer *per se* as stated in the brief). This evidence shows establishes that by 7/7/97 (after the effective dates of the patents) that declarant conceived that KD1 might be useful for treating cancer by sending the vector to Dr. Whitsett for testing. The success of the experiment was reported back to them on 9/16/97. This is the first "demonstrative evidence" for an embodiment of the claimed invention.

On page 20, Appellant alleges that it is irrelevant that Exhibit B of the first Wold declaration was a research proposal, since it "denotes the inventor's goal and provides a road map to how they planned to achieve that goal." In response, Appellant is reminded that while conception is the mental part of the inventive act, it must be capable of proof, such as by demonstrative evidence or by a <u>complete</u> disclosure to another. Conception is more than a vague idea of how to solve a problem. The requisite means themselves and their interaction must also be comprehended. See *Mergenthaler v. Scudder*, 1897 C.D. 724, 81 O.G. 1417 (D.C. Cir. 1897). The fact that Exhibit B was a research proposal indicates that the author did not comprehend the requisite means or their interaction for using ADP for treating cancer. The research proposed was aimed at discovering the requisite means and their interaction. As is evident from section B (page 3), the author did not know whether the ADP protein (11.6K protein) would kill cells on its own, and the research was aimed at determining that. Section C.3 indicates that the author also did not know whether ADP must act in concert with other adenoviral proteins, or if so, the identity of such proteins. There is clearly no suggestion in this exhibit that the author "comprehended" that

a replication competent adenoviral vector that "overexpresses" ADP was the requisite means. To the contrary, the author indicates in the last paragraph of page 5, the "the vector should probably be defective." Section D indicates that the succeeding suggestions, e.g. in section D.1, were "possible future experiments", and section D.1 indicates "exploring … whether a non-defective vector might be useful". This indicates merely that the author might carry out such an experiment, and that the author did not comprehend whether a replication competent adenoviral vector that "overexpresses" ADP was the requisite means for treating cancer.

Appellant then dismisses the fact that the inventors were not aware that KD1 overexpressed ADP until after the effective filing date of the Henderson and Little patents, by incorrectly asserting that the declaration demonstrated the preparation "of OTHER vectors with a deleted E3 region and inserted ADP gene, very similar to KD1" (emphasis in original) pointing to bullets 3 and 4 in paragraph 5 of the first Wold declaration. The adenoviruses that Appellant is referring to are *dl*753 and *dl*732, which the declaration characterizes as mutant adenoviruses with deletions (hence the "*dl*" prefix) in E3 that overexpress ADP (bullet 3). These adenoviruses are clearly not vectors and not recombinant, and were not constructed by deletion of the E3 region followed by insertion of an ADP gene. The nature and extent of the E3 deletions in *dl*753 and *dl*732 are not addressed in the declaration, so it is unclear how Appellant justifies the assertion that they were "very similar to KD1." Tollefson shows that the deletion in *dl*753 removes coding sequence for the 10.4K protein, and does not involve removal of any splice sites. No evidence has been provided relating either *dl*732 or *dl*753 to conception of the claimed method. There is certainly no evidence that the inventors had conceived using these mutants in the claimed method. The specification does not describe either mutant adenovirus, an absence which is

noteworthy given that a publication describing *dl*753 established a statutory bar to many of the cancelled claims. Also, while the specification describes deletion of coding sequence for the 10.4K protein in the context of the claimed invention in order to increase immune response to transfected neoplastic cells, it does not teach that inactivation of E3 coding regions would lead to overexpression of ADP. The only type of E3 mutation taught in the specification for ADP overexpression is the removal of splice sites. Thus, based upon the instant specification, one of skill in the art would not have expected *dl*753 to overexpress ADP.

Appellant (page 21) argues that an antedating declaration under Rule 131 need only show as much as the prior art, and there is no requirement that the 131 declaration demonstrate reduction to practice of an entire genus. Appellant asserts that the declaration shows as much as the Henderson and Little patents, focusing on CN751. In response, the claimed invention is directed to a method for treating cancer using a replication competent adenoviral vector that overexpresses ADP, not to an adenoviral vector with deletions in E3, which is all that was known of KD1 on the effective filing date of the Henderson and Little patents. Also, KD1 exemplifies only one of the various means for overexpressing ADP described in the specification (page 12-13). Consequently, it does not exemplify the entire genus being claimed. Furthermore, Henderson and Little disclose additional vector modifications relating to vectors that express ADP for use in treating cancer.

The primary thrust of these patents are adenoviral vectors whose replication is restricted to cancer cells due to the replacement of an adenoviral promoter, e.g. the E1 or E4 promoter, with a tumor-specific promoter. Expression of ADP from such vectors is described, in addition to CN751, which is not replication restricted. KD1 is also replication restricted to certain types of

tumor cells (and some normal cells) due to the *dl*01/07 mutations in the E1A gene, which prevent the E1A protein from binding the RB or p300 proteins (spec., page 6). However, the means for restricting replication to cancer cells disclosed in Henderson and Little is based upon different principles than that of *dl*01/07, i.e. they are not comparable. The instant specification does describe embodiments of the invention where the vector is replication restricted to cancer cells by replacing the E4 promoter with a tissue specific promoter (page 6), as taught in Henderson and Little, but neither Wold declaration demonstrates possession of this vector modification prior to the effective filing date of the patents. Furthermore, Henderson and Little both describe placing ADP under control of a strong heterologous viral promoter (SV40 promoter) and Little also describes including multiple copies of ADP on the vectors. Either modification would be expected to lead to ADP overexpression. The specification discloses these "means" for overexpression of ADP (page 13, lines 2-8). Neither Wold declaration demonstrates possession of replication competent adenoviral vectors having the other modifications described in Henderson and Little, much less prior to the effective filing date of the patents. Thus, the declaration does not demonstrate possession of as much as the Henderson and Little patents, but rather it shows less than the patents.

Furthermore, claim 102, unlike claim 13, is not generic with respect to the modification that leads to overexpression of ADP. It lists four different types of adenoviral vector, in the alternative, that differ with respect to the ADP gene. Choice (a) has ADP expressed under control of a heterologous promoter. Neither Wold declaration shows any evidence of conception of this embodiment prior to the filing date of the instant application, much less the effective filing date of the Henderson or Little patents. Exhibit B, section C.1, of the first Wold declaration

describes placing the ADP gene under control of the CMV promoter in a replication defective adenovirus, not a replication competent adenovirus. Section C.3 describes inserting only the ADP gene into *dl*7001, which is replication competent, but not that it would be under control of the CMV promoter; and it describes using such adenoviruses in mapping other adenoviral genes whose products collaborate with ADP, not in treating cancer. Appellant has not chosen to argue that claim 102 is separately patentable from claim 13 and its dependent claims. Claims 11-13, 32-44, 101, 103-106, and 107 stand or fall together with claim 102.

Response to arguments in section VII.C.2.

Unlike the claims under discussion in section VII.C.1., claim 60 and its dependents are not generic with respect to the ADP gene, and overexpression of ADP is not required. Instead, claim 60 is directed to the use in treating cancer with one of four different types of adenoviral vector listed in the alternative. Of the four, the only types under consideration here are the use of vectors where an ADP gene is under control of a heterologous promoter (claim 60, part (a), claims 68 and 69) and where at least one splice site is deleted from the E3 region (claim 60, part (b), claims 72-75). Appellant has chosen to argue all of claims 60, 61, 68, 69, 72-75, 97-99 and 107 together. These claims stand or fall together.

Appellant refers to their arguments in section VII.C.1 as showing prior conception of the claimed invention. These arguments are unconvincing for the reasons set forth above in the response to the arguments present in section VII.C.1 (and its subsections) of the brief. Briefly, the claims are not directed to adenoviral vectors, but to a method of using adenoviral vectors to treat cancer, and the declarations fail to show evidence of conception of the claimed method prior to the effective filing date of the Henderson and Little patents.

With respect to the first type of adenoviral vector where the ADP gene is under control of a heterologous promoter, neither Wold declaration shows any evidence of conception of this embodiment prior to the filing date of the instant application, much less the effective filing date of the Henderson or Little patents. Exhibit B, section C.1, of the first Wold declaration describes placing the ADP gene under control of the CMV promoter in a replication defective adenovirus, not a replication competent adenovirus, as required by the claims. Consequently, claims 60, 61, 97-99 and 107, which embrace this embodiment, and claims 68 and 69, which are specifically directed to this embodiment, are clearly anticipated by Henderson and Little.

With respect to the second type of adenoviral vector where the sequence for at least one E3 splice site is removed, Appellant states that the declaration shows that the inventors conceived of preparing vectors with E3 deletions plus reinsertion of the ADP gene. This is not the same as the concept of deleting an E3 splice site. Neither Wold declaration provides evidence of conception of this embodiment prior to the filing date of the instant application, much less the effective filing date of the Henderson or Little patents. The fact that splice sites have been deleted in KD1 does not show that the inventors had comprehended that removal of one or more E3 splice sites in an adenoviral vector would make it useful for treating cancer. Furthermore, the only evidence provided in the first Wold declaration relating to the treatment of cancer is Exhibit B. KD1 appears to relate most to the experiments proposed in section C.3 of Exhibit B, where the authors proposed mapping adenoviral genes outside of the E3 region that express proteins that collaborate with ADP (11.6K protein) in promoting cell death. The authors are not proposing here that such replication competent vectors themselves are useful for treating cancer. It remains that the declarations do not provide evidence for conception either of using a generic replication

competent adenoviral vector that has had at least one E3 splice site removed or of using KD1 specifically in a method of treating cancer.

In the sentence bridging pages 23 to 24 of the brief in relation to whether a vector in which E3 had been deleted and ADP reinserted, e.g. KD1, overexpresses ADP, Appellant states: "although this had already been shown by them with another such vector." It is unclear what "such vector" Appellant is referring to here. If Appellant is referring to *dl*732 or *dl*753, the first Wold declaration clearly indicates that these are deletion mutants, not recombinant vectors. As indicated above in the response to section VII.C.1.c.(4) of the brief, Tollefson shows that the deletion in *dl*753 removes coding sequence for the 10.4K protein, and does not involve removal of any splice sites. Thus, claims 60, 61, 68, 69, 72-75, 97-99 and 107 do not embrace using *dl*753 in the method. There is no evidence of record describing the nature of the E3 deletion in *dl*732, much less whether any E3 splice sites were deleted.

Response to arguments in section VII.D.

Appellant (subsection 1) refers to their arguments (section VII.C.1) as showing prior conception of the claimed invention before the effective filing date of the Henderson and Little patents, and Freytag alone does not teach the claimed invention. These arguments are unconvincing for the reasons set forth above in the response to the arguments present in section VII.C.1 (and its subsections) of the brief. Briefly, the claims are not directed to adenoviral vectors, but to a method of using adenoviral vectors to treat cancer, and the declarations fail to show evidence of conception of the claimed method prior to the effective filing date of the Henderson and Little patents. Furthermore, the declarations provide no evidence that the

inventors had conceived of combining treatment with an adenovirus with radiation or chemotherapy.

Appellant also argues (subsection 2) that there is no motivation to combining the teachings of Freytag with those of Henderson or Little. Appellant asserts that Freytag discloses using radiation specifically in conjunction with an adenovirus comprising a suicide gene. However, Appellant is attempting to de-emphasize the fact that Freytag teaches combining the modalities of virotherapy with replication competent adenovirus, suicide gene therapy, and radiation in treating cancer. The suicide genes are included in a replication competent adenovirus. Henderson and Little are directed to virotherapy with replication competent adenovirus, and teach that expression of ADP enhances the cytolytic effect. Furthermore, both Henderson (col. 27) and Little (col. 21) teach embodiments including sequences encoding a prodrug converting enzyme on their vectors. Freytag (see abstract) teaches that including genes encoding CD and HSV-1 TK, which are prodrug converting enzymes, in an oncolytic adenovirus provides three benefits: sensitizing tumors to radiation, enhancement of the cytolytic effect of the virus and to suppress viral replication to control viral spread. These teachings provide ample motivation to modify the adenoviral vectors of Henderson and Little with the suicide gene combined with radiation for treating cancer, i.e. it would be expected to increase the efficacy of the cancer treatment. With respect to chemotherapy, Freytag (page 1324, col. 1) teaches that the suicide gene therapy avoids systemic toxicity associated with conventional chemotherapy using 5-flurouracil. The method of Freytag involves administration of gancyclovir and 5-fluorocytosine, which is chemotherapy.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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